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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/671,921	EINAT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 26-28* is/are pending in the application.

4a) Of the above claim(s) *3,4,8,9 and 12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,10,11 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 4/8/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Further correspondence in this application is properly addressed to Examiner Richard Schnizer, whose contact information is given at the end of this Action.

An amendment was received and entered on 3/15/07.

Claims 21-25 were cancelled, and claims 26-28 were added as requested.

Applicant's election with traverse of group 3 is acknowledged. Traversal is on the grounds that search and examination of inventions 1-3 would not constitute a serious burden. This is not found persuasive because Applicant's argument is not supported by evidence or reasoning that would indicate that the there would be no undue burden in searching and examining these three inventions together.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20 and 26-28 remain pending in the application.

Claims 3, 4, 8, 9, and 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/15/07.

Claims 1, 2, 5-7, 10, 11, and 26-28 are under consideration in this Office Action, to the extent that they read on the elected invention, i.e. methods of treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of human MKLP1, wherein the inhibitor is an siRNA oligonucleotide comprising the sequence of SEQ ID NO: 4.

Specification/Drawings/Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **Fig. 3 discloses a nucleotide sequence of greater than 9 nucleotides that is not accompanied by a SEQ ID NO.** If this sequence is listed in the current Sequence Listing, then the specification or drawing should be amended to include the appropriate SEQ ID NO in the appropriate passage. If this sequence is not in the current Sequence Listing, then Applicant must provide:

An substitute computer readable form (CRF) copy of the "Sequence Listing".

An substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951

• For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.

• Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5-7, 10, 11, and 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5, 7, 10, and 26-28 are indefinite in their recitation of "apoptosis-related disease" because it is unclear what is the nature of the relationship between apoptosis and the disease. In view of the specification as a whole, the invention is intended to promote apoptosis. However, the term "apoptosis-related" would be reasonably understood to mean diseases that are caused by apoptosis, rather than those in which it is deficient. It is unclear how the disease must be related to apoptosis in order to be embraced by the claims, so one of skill cannot know the metes and bounds.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-7, 10, 11, and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 2, 5, 6, and 26-28 are drawn to methods of treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of human MKLP1, wherein the inhibitor is an siRNA oligonucleotide comprising the sequence of SEQ ID NO: 4. Claim 6 limits the breadth of the disease to a cancer. Claims 7, 10, and 11 are drawn to methods of potentiating a chemotherapeutic treatment of an apoptosis related disease comprising administering to a subject a chemotherapeutic agent and a therapeutically effective amount of an siRNA oligonucleotide comprising the sequence of SEQ ID NO: 4. Claim 11 limits the breadth of the disease to a cancer. The scope of diseases embraced claims not limited to cancer includes degenerative neurological diseases such as Alzheimer's, Parkinson's, stroke, epilepsy, depression, ALS, Huntington's disease, of T-cell death in AIDS patients, transplant-associated cell death, hypertension, aneurysm rupture, thrombus, angioma, cardiac arrest, septic shock, spinal cord trauma, and others listed at page 21, lines 4-20. The specification provides no nexus between apoptosis and any of stroke, epilepsy, depression, hypertension, aneurysm rupture, thrombus, angioma,

cardiac arrest, septic shock, spinal cord trauma. Accordingly it is left to one of skill in the art to establish such a nexus and to determine whether and how one could use MKLP1 siRNA to treat such disorders.

The MKLP1 gene was identified as a gene that modulates apoptosis negatively, and so Applicant considers it to be a target for potential cancer drugs. Briefly, HeLa cells were transfected with a library of episomal cDNA antisense expression vectors, the cells were then treated with an anti-Fas antibody that triggers Fas-mediated apoptosis in HeLa cells. Vectors encoding antisense molecules that potentiated apoptosis were identified, including antisense against MKLP1. Based on this screening experiment, Applicant proposes that siRNA directed against MKLP1 mRNA will promote apoptosis.

However, those of skill in the art appreciate that there are other pathways to apoptosis besides the Fas-mediated pathway. Accordingly skilled artisans would not accept that inactivating an inhibitor of Fas-mediated apoptosis would necessarily affect Fas-independent pathways. Further, because many chemotherapeutic drugs act by Fas-independent pathways, one of skill would not expect an inhibitor of Fas-mediated apoptosis to potentiate apoptosis with chemotherapeutic drugs as broadly claimed. For example, Eischen et al (Blood 90(3): 935-943 1997) tested the hypothesis that chemotherapeutic agents induce death by activating the Fas/FasL pathway, and found that etoposide, doxorubicin, topotecan, cisplatin, methotrexate, staurosporine, and gamma irradiation all function through Fas-independent pathways. Eischen postulated that Fas-independent and Fas-dependent apoptosis pathways converge on common downstream effector molecules. See abstract. However, the instant specification fails

to teach if MKLP1 acts before or after the convergence point, such that one of skill in the art could not conclude that MKLP1 would potentiate apoptosis by chemotherapeutic agents, or that MKLP1 would potentiate Fas-independent apoptosis in general.

Furthermore, those of skill in the art appreciate that in vivo treatments requiring delivery of siRNA molecules are highly unpredictable. Those of skill in the art at the time of the invention, and after the invention, recognized significant obstacles related to the predictability of inhibiting expression of a target gene *in vivo* by RNA interference (RNAi), particularly in regards to the *in vivo* targeting and delivery of specific nucleic acids that mediate RNAi to the appropriate cell/organ, at a bio-effective concentration and for a period of time such that said molecule is effective in inhibiting expression of a target gene. Indeed, nucleic acid based therapies at the time of filing were highly unpredictable and while it is recognized that introduction of dsRNA targeted to a specific gene may result in expression inhibition, the successful delivery of dsRNA to a target cell *in vivo*, such that the requisite biological effect was provided to the target cells/tissues/organs, must be determined empirically.

The state of the art at the time of filing shows that RNA interference was recognized as not enabled for therapeutic purposes. (See for example, Caplen 2003, Expert Opin. Biol. Ther. 2003, Vol. 3, pp. 575-586; Coburn et al. 2003, Journal of Antimicrobial Chemotherapy. Vol. 51, pp. 753-756; Agami et al. 2002 Current Opinion in Chemical Biology. Vol. 6, pp. 829-834) for a review on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pp. 503-514) stated, "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA", and in column 2 of the same page, "[a]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Caplen (2003) taught that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (pg. 581).

Coburn et al. (2003) taught that the major impediment to using RNA interference as a therapeutic is that suppression of gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example page 754, first column, last paragraph).

Check (Nature, 2003, Vol., 425, pp. 10-12) reported "...scientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up." (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " ...'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page, "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

After the time of the invention, Zhang et al (Current Pharmaceutical Biotechnology 2004, Vol. 5, pp.1-7) reviewed the state of the art with regard to RNAi, and stated "[u]se of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Thus it is abundantly clear that it was not routine prior to and after the time of the invention for those of skill in the art to perform therapy by delivery of siRNA to target cells in vivo.

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed does not disclose any delivery formulations or techniques that were not available in the prior art, including delivery of expression vectors encoding siRNA, and so does not adequately address the state of the art at the time of the invention with regard to siRNA delivery to target cells in vivo. The specification provides no working example of therapy, no guidance as to what amount of siRNA comprising SEQ ID NO:4 is an effective amount, and no guidance regarding administration routes or frequency, except possibly by improper reference to non-patent publications (see MPEP 608.01(p)). Also, as noted above, the specification fails to establish whether or not many diseases listed in the specification are actually related to apoptosis, leaving this to one of skill in the art to determine.

Note also that the specification indicates that methods useful for delivering antisense oligonucleotides are also useful for delivering siRNA. However, at the time of the invention these techniques were problematic for in vivo delivery. For example, Agrawal et al (Mol. Med. Today 6:72-81, 2000) stated "[t]he cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....in vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discussed these factors in relation to antisense, but they would also apply to

dsRNA. Due to differences in the physiological conditions of a cell in vitro versus in vivo, the uptake and biological activity observed in vitro would not predictably translate to in vivo results (see p 79-80, section entitled "Cellular uptake facilitators for in vitro studies").

Given the recognized unpredictability in the art of nucleic acid therapeutics, one of skill would still require specific guidance to practice the claimed methods *in vivo* in any organism or any mammal, with the resultant specified biological effect of treating or preventing an apoptosis-related disease, or cancer. However, the specification does not provide either examples or the required guidance to allow one of skill in the art to reliably and predictably obtain success using the claimed methods *in vivo* in mammals or any other animal. The specification does not overcome the art recognized obstacles to *in vivo* RNAi, particularly in terms of specific targeting and delivery of the dsRNA to a whole organism. As a result one of skill in the art would have to perform undue experimentation in order to practice the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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